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Declining Blood Lead Levels and Cognitive Changes in Moderately Lead-Poisoned Children

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Objective.—To determine whether chelation therapy or biochemical changes during a lead-lowering intervention was associated with changes in cognitive functioning of moderately lead-poisoned children. It was hypothesized that cognitive performance would improve as blood lead level declined over time.

Design.—Short-term intervention study with measures obtained before and after intervention.

Setting.—Hospital specialty clinic and university research center.

Patients.—A total of 154 previously untreated children referred to clinic with blood lead levels between 1.21 and 2.66 μmol/L (25 and 55 μg/dL) at time of enrollment. Ages ranged from 13 to 87 months.

Intervention.—Enrolled children were treated with edetate calcium disodium (EDTA) if eligible and/or with orally administered iron supplement if iron deficient. For all children, housing inspections and abatement procedures were performed as necessary.

Main Outcome Measures.—Score on Bayley Mental Development Scale or Stanford-Binet Intelligence Scale (4th edition).

Results.—There was no effect of edetate calcium disodium treatment per se. In the short term (7 weeks), changes in blood lead levels were not related to changes in cognitive scores. In the long term (6 months), however, changes in performance were significantly related to changes in blood lead level, even after controlling for confounding variables. The standardized score increased 1 point for every decrease of 0.14 μmol/L (3 μg/dL) in blood lead level.

Conclusion.—The results suggest an association between decreases in blood lead level and cognitive improvements in moderately lead-poisoned children.

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THE EFFECTS of low to moderate levels of lead on the brain and cognitive functioning of children has become an important research issue in the last 20 years. Although the issue is a complex one,[1] data have accumulated suggesting that even low levels of lead affect children's performance on standardized evaluations of cognitive functioning. The numerous cross-sectional studies to date converge on a strong conclusion that there is a negative association between lead levels and intellectual performance.[2] Two examples show the general size of the association. Needleman et al[3] reported that intelligence test scores were approximately 4.5 points lower for school children with moderately high dentine lead levels than for children with low dentine lead levels. Fulton et al[4] found a 5.8-point difference in scores on the British Ability Scales between their highest and lowest blood lead (BPb) groups (range, 0.14 to 1.64 μmol/L [3 to 34 μg/dL]). The associations observed in these studies remained significant when an array of appropriate covariates were accounted for, although this was not necessarily the case in other studies.

See also pp 1614, 1647, and 1679.

In the past decade, these cross-sectional studies have been supplemented by a number of large prospective studies in which exposure to lead in utero and later neurobehavioral functioning have been investigated.[5-11] The investigators in such studies gathered information about the timing and extent of the exposure as well as about many other important social factors that affect neurobehavioral development. In many of these studies,[5,6,8] but not all,[10] there has been a significant negative association between prenatal exposure to lead and early neurobehavioral functioning after control for relevant background factors. The relationship of cognitive functioning to prenatal exposure seems to diminish with time[7,9,11] but may be replaced by an association between postnatal exposure and cognitive performance. McMichael et al,[11] for example, found that a cumulative index of postnatal lead exposure was related to scores on the McCarthy Scales at 4 years of age. Bellinger et al[7] found that McCarthy General Cognitive Index at 4 to 5 years of age was not related to the groups

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stratified by prenatal lead level but was related to lead levels at 2 years of age. These investigators have not documented a significant association between concurrent BPb levels and performance in the first few years of life after potential confounders were taken into account; the significant associations seem to be between performance and either cumulative or prior BPb levels.

There are a number of difficulties with trying to isolate the causal effects of lead from other potential influences.[1] Meta-analyses[2] cannot address the issue of causation, and although many recent studies have involved a careful consideration of confounding variables, the control for these variables is necessarily imperfect. The critical process of obtaining convergent evidence requires that observational studies be supplemented by studies in which lead level is specifically manipulated. Investigations of primates systematically exposed to lead demonstrate that there are small but significant effects of low to moderate levels of lead on behavior.[12-16] Although such studies cannot be conducted in humans, it is possible to examine the correlates of decreasing lead burden as a result of intervention in children.

Very few studies of the effects of chelation treatment on neurobehavioral outcomes have been conducted, but two earlier studies by David and colleagues[17,18] provide suggestive data. They found that the parent and teacher ratings of hyperactive children with a history of lead toxicity improved after 12 weeks of treatment with an oral chelating agent. However, these investigators did not address the issue of global cognitive changes, the main outcome variable in other studies, and the number of subjects was small. Therefore, the current report involves analyses of data from a large study of neurobehavioral functioning in children who were subject to systematic medical and environmental intervention because of moderately high BPb levels.

In a previous article from the current study,[19] it is suggested that chelation treatment with edetate calcium disodium (EDTA) was not significantly related to changes in BPb values. Levels of BPb decreased in both groups of children regardless of chelation therapy during the course of the study, and there was considerable interindividual variation in the amount of change. For this article, we analyzed the effects of edetate calcium disodium chelation treatment, but more emphasis was placed on change in BPb level regardless of the reason for the change. The goal was to examine the relationship between changes in BPb level and changes in performance on standardized assessments of cognitive functioning. Because we examined both short-term (7-week) and long-term (6-month) changes, we were able to examine the concurrent vs cumulative effects of declining BPb levels.

METHODS

The study involved two forms of medical intervention: (1) chelation treatment for an excessive body burden of lead as defined by the urinary excretion of lead during an 8-hour edetate calcium disodium lead mobilization test (LMT),[20,21] conducted on all enrolled children at time 1; and (2) iron supplementation for children who were iron deficient or depleted (ferritin level, <16 μg/L). Iron was important for theoretical as well as clinical reasons because it is potentially both a confounder and a mediator of the effects of lead.[22,23] Children were enrolled in the study if their BPb levels at the time of enrollment were between 1.21 and 2.66 μmol/L (25 and 55 μg/dL), and their erythrocyte protoporphyrin (EP) levels were greater than 0.65 μmol/L. The study was approved by the local institutional review boards, and consent was obtained from the parents or guardians of all participating children. If the child's LMT result was positive, treatment consisted of 5 days of in-hospital administration of edetate calcium disodium; if the child was iron deficient, an orally administered iron supplement was prescribed. The enrolled children could be given both forms of treatment, neither form, or either one of them alone. For all children, there were sequential inspections of the home and largely successful attempts to eliminate exposure to lead-based paint through existing housing codes.

The children's cognitive development and behavior were evaluated at three time points: time 1—approximately 1 week after enrollment and before the treatment course was determined; time 2—approximately 7 weeks after the first visit; and time 3—approximately 6 months after the first visit. The dependent variable was the child's performance on a global test of cognitive functioning. Assessors were blinded to the treatment status of children and to their BPb levels.

Sample

The subjects of this report were 154 children selected from the 195 previously untreated children enrolled in the study. The selection criteria were as follows: (1) complete data for BPb and EP levels, cognitive functioning, and all background factors except mother's IQ at time 1; and (2) no outlying values on the main biochemical or cognitive variables at time 1. Preliminary analyses showed that BPb level greater than 2.46 μmol/L (51 μg/dL), EP level greater than 4.71 μmol/L, ferritin level greater than 50 μg/L, and cognitive test score greater than 111 were statistical outliers for our sample. In the SYSTAT program used for these analyses, an outlying value was defined as 25th percentile score minus 1.5 times the range between the 25th and 75th percentile scores or the 75th percentile score plus 1.5 times that range. For example, the 25th and 75th percentile scores for BPb level were 26 and 36; therefore, outliers were any value outside of the range between 11 and 51.

When the short-term changes (time 1 to time 2) and long-term changes (time 1 to time 3) were analyzed, the numbers of subjects were reduced to 145 and 129, respectively, because the data at either time 2 or time 3 were incomplete. There were 126 children with complete data at all three times.

Procedures

Within 1 week after enrollment, each child was seen for a battery of cognitive and behavioral tests. Only the global test of cognitive functioning will be dealt with here. Within 3 days of this evaluation, each child underwent an LMT and a newly obtained blood sample was analyzed for BPb, EP, and ferritin levels. Based on the results of the LMT, the child was either hospitalized for a 5-day course of treatment or did not receive treatment.[20] An orally administered iron supplement (6 mg/kg per day) was prescribed if indicated, and a housing inspection was conducted for all children. Except for the LMT, which depended on current BPb level, this process was repeated approximately 7 weeks later whether or not the child had been hospitalized for edetate calcium disodium chelation treatment and again approximately 6 months after enrollment. The cognitive and biochemical measures were therefore closely linked in time.

Measures

The outcome measure was a global index of cognitive functioning. Because of the age range of the children, it was necessary to use two different tests. For the younger and the more immature older children, we administered the Bayley Scales of Mental Development.[24] The Bayley is standardized for children aged 30 months and younger and yields a single score, the Mental Development Index. The other test, the Stanford-Binet Intelligence Scale (4th edition),[25] yields a composite IQ score. Both tests provide standard scores with a mean of 100 and an SD of 16.

The Stanford-Binet is intended for children as young as 2 years of age but was too difficult for many of the children in our sample. Therefore, we administered the Bayley to 24 children who were older than the standardization sample. These children were not at the raw score ceiling of the test even on their last visit. In the absence of norms for children older than 30 months of age, we estimated Mental Development Index by subtracting 3 Mental Development Index points from the 30-month norms for every month over 30, our own extrapolation from the relationship of raw scores and standardized scores between 24 to 30 months of age.

Because of this use of the Bayley, the wide age range, and the fact that 40% of the tests were administered in Spanish, we estimated the reliability of the tests in our sample by correlating the global cognitive scores at time 1 with those at time 2 and controlling for age at time 1, the presence of edetate calcium disodium chelation treatment between the two visits, and iron status at time 1. The reliability coefficients by particular test and language of administration were all reasonably high (.73, .71, .83, and .79 for the English Bayley, Spanish Bayley, English Stanford-Binet, and Spanish Stanford-Binet, respectively). The correlations for separate age groups were .74, .79, and .82, respectively, for the children aged 24 months and younger, the children from 25 through 41 months of age, and children older than 41 months of age. Within the middle age group, the children were either administered the Bayley at all times, the Stanford-Binet at all times, or switched from the Bayley to the Stanford-Binet if their functioning warranted it. The reliabilities for these subgroups were .73, .83, and .71, respectively.

The independent variables were categorical when the effects of chelation treatment were tested and continuous when the relationship between biochemical and cognitive changes was tested. Blood lead level (95% confidence limit, <0.05 μmol/L [1.0 μg/dL]) was measured by graphite furnace atomic absorption spectroscopy.[21,22] The EP level was determined by the extraction method of Piomelli.[23] Our laboratory participates successfully in the proficiency testing programs of New York, NY, and the Centers for Disease Control and Prevention, Atlanta, Ga. Ferritin was measured by radioimmunoassay. The intra-assay and interassay coefficients of variation were 3% and 4%, respectively.[23] Ferritin levels were missing at some time points for eight children whose data were otherwise complete. To replace these missing data, we regressed ferritin level on age and used the resulting values to estimate missing ferritin values.

A set of background variables served as covariates in the analyses. These included age, sex, birth order, household size, socioeconomic status, score on the Caldwell HOME inventory, the number of prenatal complications, the number of perinatal complications, and the language of test administration (Spanish/English). The language variable was strongly related to race because most of the sample children were either black or Hispanic, but it was more strongly related to the other variables than race. Age, sex, and language of test administration were kept as separate variables. The other variables were reduced by a principal components analysis; on the basis of the factor loadings, HOME score and socioeconomic status were standardized and added, as were birth order and household size; the number of prenatal and perinatal complications were simply added to provide a single index of complications. Because all potential covariates were related to either the cognitive or biochemical variables, we used all of the variables in the reduced set as covariates in subsequent analyses. Maternal IQ[27] was tested separately as a covariate because there were more missing data for this variable, but it never diminished the relevant effects and will not be mentioned further.

Analysis Strategy

We used repeated measures analysis of variance descriptively to determine whether changes in mean levels of the biochemical and cognitive variables over time were significant. In dealing with the effect of edetate calcium disodium chelation treatment on cognitive index (CI), treatment with edetate calcium disodium was entered as a categorical independent variable in an analysis of covariance with initial CI controlled for: this is an example of "regressed change" and is preferable to a simple analysis of variance of change.[28] Because of the wide age range and the relationship of age to the biochemical variables and the CI, age at time 1 was included in all equations. The effect of iron supplementation and its interaction with chelation treatment were also tested. For the short-term and some long-term analyses, all children were coded as either treated or untreated; number of treatments was ignored. For other analyses of long-term effects, the children who were never treated were compared with those who were treated only once between time 1 and time 2. For the final analyses in each case, all covariates were entered because no interactions between the covariates and treatment were significant.

For the main analyses, we examined regressed change in CI in relation to changes in BPb level during the study period. As with the analyses of covariance, the dependent variable was change in CI; the major independent variable was change in BPb level with control for age, the initial level of BPb, and initial CI. Possible interactions between age and change in BPb level were tested, as were possible interactions between initial BPb level and change in BPb level. In the next step, change in ferritin level was entered as a covariate and potential confounder. In the third and final step, all covariates were entered to determine whether the observed effect was still present. Interactions between the covariates and change in BPb level were tested but found to be nonsignificant. Significant effects were tested for the effects of individuals with undue influence; none were found.

RESULTS

The age of the children in the sample at the first visit ranged from 13 to 87 months. The children were almost all either black (37%) or Hispanic (58%), and 57% were boys. Socioeconomic status ranged from 8 to 60 on the 4-factor Hollingshead scale where 60 is the maximum; the median was 17. In terms of early history, 53% had at least two prenatal or perinatal complications. These data suggest that the sample consisted of children who were disadvantaged and at risk for developmental delays. Not surprisingly, therefore, the median score on either the Bayley Scales of Infant Development or the revised Stanford-Binet at time 1 was 79.5, with a range from 47 to 111; the median maternal IQ as measured in 126 of the mothers was 89, with a range from 57 to 120.

The BPb levels of the sample at time 1 (1 week after enrollment) ranged from 0.63 to 2.22 μmol/L (13 to 46 μg/dL) with a median BPb level of 1.45 μmol/L (30 μg/dL). The EP levels ranged from 0.51 to 4.12 μmol/L with a median EP level of 1.49 μmol/L. Ferritin levels ranged from 2 to 49 μg/L; 60 (39%) of the 154 children were iron deficient and treated accordingly. Of the 154 children, 93 (60%) were not eligible for treatment with edetate calcium disodium while they were in the study: 35 (23%) were treated only once; 19 (12%) were treated twice; and seven (5%) were treated at all three time points. Only 14 (9%) of the children were treated with both iron and edetate calcium disodium at time 1.

All of the analyses reported herein were also performed with EP level as an independent variable. These analyses led

to similar inferences as the analyses with BPb level, and there was no evidence that EP level was independently associated with cognitive functioning. Therefore, we report only the findings for BPb level.

Relationship Among Cognitive, Biochemical, and Background Variables at Time 1

The first question is whether BPb or ferritin level was related to the CI at time 1. The CI at time 1 was regressed on age and either BPb or ferritin level (Table 1). Blood lead level was not related to the CI at time 1, and there was no interaction between BPb level and age or the particular test used. In contrast, cognitive performance was significantly related to ferritin level even with the addition of the set of background factors (partial correlation, .26); there were no interactions between ferritin level and age or the particular test used. As can be seen in Table 1, every microgram per liter increase in ferritin level represents about 0.3 points in the CI. There was no interaction between BPb and ferritin levels.

Description of Changes Over Time in Biochemical and Cognitive Variables

Table 2 presents the means of the biochemical variables and the CI for the 126 children who provided data at all three time points. Blood lead levels decreased significantly. Ferritin level increased significantly, but the separate means for the iron-sufficient and iron-deficient children showed that ferritin levels increased significantly only for the children who were deficient at time 1.

The mean CI increased to a small but significant degree over time. Table 2 also shows the results separately for those children given the Bayley or the Stanford-Binet at all three time points. The children given the Bayley changed very little while the others improved. Since, by definition, these two groups differed in age, a repeated measures analysis of variance using the data from the entire group was used to test the effects of age on the mean CI as well as on changes over time. Younger children not only had lower scores overall, F (1, 122)=8.8, $P<.06$, but there was a significant interaction between age and change over time, with the scores of the youngest children declining and the scores of older children increasing, F (2, 244)=7.5, $P<.001$. In disadvantaged groups of children, it is not uncommon to see a downward trend in Mental Development Index around 2 years of age.[2] The increase in mean scores from time 1 to time 2 observed in the older children may be due to warm-up or practice effects.

The Effects of Edetate Calcium Disodium Chelation Treatment

Treated children were on average 8 to 9 months older than untreated children. In analyses of covariance with age and initial CI controlled, the main effect of edetate calcium disodium treatment was nonsignificant between time 1 and time 2 with and without other background factors controlled, F (1, 186)<1.0, P=.48. The effect of edetate calcium disodium treatment in the long term was also nonsignificant, F (1, 120)<1.0, P=.94. In addition, the unchelated children were not different in the long term from those who were chelated only between time 1 and time 2, F (1, 98)<1.0, P=.73. In none of these cases was there any evidence of an interaction between edetate calcium disodium treatment and iron supplementation. Table 3 presents the mean CIs for these three comparisons. Simple, unadjusted analyses of variance yielded the same results.

The Relationship of Behavioral Changes to Biochemical Changes

The central question of this report therefore is: In what way were cognitive changes related to changes in the biochemical variables, particularly BPb level? In the short term, the change in CI was not related to change in BPb or ferritin concentrations. In the long term, however, changes in BPb level were related in the expected direction to changes in the CI from time 1 to time 3 (Table 4); that is, CI increased as BPb level decreased. There were no significant interactions between change in BPb level and age or initial level. The regression coefficient (−.310; P=.05) increased slightly when change in ferritin level and the set of background covariates were added (−.334; $P<.05$). In general, these results suggest that the CI increases approximately 1 point for every decrease in BPb level of 0.14 μmol/L (3 μg/dL). Changes in ferritin level were, however, not related to changes in CI (Table 4).

To translate these findings into more concrete terms, the children were divided into subgroups according to the median change in BPb level during the 6 months. Change in BPb level ranged from a decrease of 1.45 μmol/L (30 μg/dL) to an increase of 0.39 μmol/L (8 μg/dL). Children who were below the median (decreases >0.34 μmol/L

Table 1.—Relationship of Cognitive Index (CI) to Biochemical Variables at Time 1 (n=164)*

Independent Variable†	Covariates	Partial Correlation	Regression Coefficient	P
Blood lead level	Age alone	.08	.113	.50
	Age plus set of background factors	.02	.047	.78
Ferritin level	Age	.30	.381	<.001
	Age plus set of background factors	.28	.394	.002

*Time 1 occurred approximately 1 week after enrollment and before treatment course was determined.
†The dependent variable across the CI at time 1. The basic regression equation is as follows: CI = Constant + Age + Blood Lead or Ferritin (+ Background Factors).

Table 2.—Description of Changes During Course of Study for Children Seen at All Three Time Points (n=126)*

	Mean (SD)		
	Time 1	Time 2	Time 3
Blood lead level, μmol/L [μg/dL]	1.50 (0.31) [31.2 (6.5)]	1.30 (0.30) [26.9 (6.3)]	1.15 (0.31) [23.9(6.5)]†
Ferritin level, μg/L	19.4 (10.7)	20.0 (10.5)	24.8 (11.8)
Deficient, time 1 (n=52)	9.8 (3.3)	14.2 (7.8)	19.3(8.0)‡
Sufficient, time 1 (n=74)	26.1 (8.9)	24.1 (10.2)	28.4 (12.0)
Cognitive index	78.0 (13.0)	83.1 (13.6)	82.6 (13.3)
Bayley score (n=39)	79.2 (14.0)	78.4 (14.1)	76.6 (13.9)
Stanford-Binet score (n=63)	83.6 (10.2)	87.0 (10.3)	88.1 (11.2)

*Time 1 occurred approximately 1 week after enrollment and before treatment course was determined; time 2, approximately 7 weeks after first visit; and time 3, approximately 6 months after first visit.
†Repeated measures analysis of covariance with age as the covariate, F (2, 248)=17.3 and $P<.001$.
‡F (2, 100)=4.7, P=.008.

Table 3.—Change in Cognitive Performance According to Chelation Treatment Status*

	Cognitive Index (CI), Mean (SD)		
	Time 1	Time 2	Time 3
Short-term changes in CI			
Untreated (n=91)	78.5 (12.8)	82.8 (12.4)	...
Treated (n=54)	79.4 (14.6)	82.9 (15.1)	...
Long-term changes in CI			
Untreated (n=80)	78.8 (11.4)	...	81.5 (12.3)
Treated (n=49)	79.2 (15.1)	...	83.8 (14.8)
Treated once (n=27)	79.8 (14.5)	...	82.6 (14.2)

*Time 1 occurred approximately 1 week after enrollment and before treatment course was determined; time 2, approximately 7 weeks after first visit; and time 3, approximately 6 months after first visit.

Table 4.—Relationship of Biochemical Changes to Changes in Cognitive Performance During 6-Month Period*

Independent Variable†	Covariates	Partial Correlation	Regression Coefficient	P
Change in BPb level from time 1 to 3	Age, CI1, BPb1	−.17	−.316	.05
	With addition of Fer change	−.18	−.336	.04
	With addition of background factors	−.18	−.334	<.05
Change in Fer level from time 1 to 3	Age, CI1, Fer1	−.02	.025	.78

*Time 1 occurred approximately 1 week after enrollment and before treatment course was determined; time 3, approximately 6 months after first visit; CI1, Cognitive index at time 1; BPb1, blood lead level at time 1; Fer1, ferritin level at time 1; CI3, CI at time 3; BPb3, BPb level at time 3; and Fer3, Fer level at time 3.

†The dependent variable equals change in CI from time 1 to time 3. The coefficients were derived from a regressed change model. The equation for the final step in the first analysis was CI3 = Constant + Age + CI1 + BPb1 + BPb3 + Fer1 + Fer3 + Background Factors. The coefficient would be identical if CI3, BPb3, and Fer3 were replaced with raw changes from time 1 to time 3 and initial values were controlled.

[7 μg/dL]; n=60) showed an increase of 5.4 points on the CI. Children at or above the median were divided at no change to separate the data for children whose BPb levels did not change or actually increased: the children between the median and no change (decreases of 0.05 to 0.34 μmol/L [1 to 7 μg/dL]; n=58) improved 3.0 points; the group whose BPb levels stayed the same or increased (n=16) declined in CI by 2.6 points. These patterns in raw score change are illustrative only but are consistent with the previous regression analyses showing an association between BPb level and CI.

An alternative explanation of the observed association is that a third variable contributed to changes in BPb level and was independently related to improvements in cognitive scores. For example, enhanced nutritional status may facilitate the excretion of lead and, in parallel, be correlated with levels of alertness or attention that make it possible for the child to benefit from repeated testing. Because iron status could conceivably play such a role, we examined the iron status of the subgroups described herein. There were no differences in the proportion of children who were iron sufficient at the time of enrollment across the BPb change groups (58%, 60%, and 56%). In addition, when the children who were iron deficient at enrollment were compared with those who were iron sufficient, there was no evidence that a larger mean decrease occurred in BPb level during the 6 months in the iron-sufficient group (iron deficient, BPb level=−0.23 μmol/L [−4.8 μg/dL]; iron sufficient, BPb level=−0.36 μmol/L [−7.5 μg/dL]). Nor was there a difference in pattern of cognitive change over time, although there was a mean difference in absolute level (iron deficient, CI=75.8, 80.7, and 80.2; iron sufficient, CI=81.4, 84.8, and 84.2).

COMMENT

The first question we addressed was whether there were any relationships between the biochemical variables and cognitive functioning at time 1. The only significant relationship was a moderate correlation of test performance with ferritin levels such that every increase of 3 μg/L in serum ferritin level was related to an increase of 1 point on the CI. The fact that we did not see a relationship of BPb level to cognition in this initial cross-sectional analysis is consistent with the data from the prospective studies where children less than 5 years of age have been observed.[5,7,11] Although there is little evidence from those studies that BPb levels are concurrently related to general cognitive performance in the early years, there is evidence for a cumulative or delayed association between cognition and postnatal exposure to lead.

The fact that there was no effect of chelation treatment may be related to the presence of other interventions, such as abatement procedures in the home. In the absence of chelation therapy, a reduction or elimination of exposure may have led to decreases in BPb levels. Such decreases may have occurred for both chelated and nonchelated children, thereby obscuring the effect of chelation treatment per se. The lack of a treatment effect may also be related to the fact that all children received a modest dose of edetate calcium disodium during the LMT at time 1. In addition, only one outcome variable was assessed here, and the lack of effect of chelation on CI cannot be generalized to other measures of cognitive change.

Even if we had found a significant effect of edetate calcium disodium treatment at the initial measurement, it would have been important to show a relationship between biochemical and cognitive changes over time. Based on the assumption that the children's cognitive functioning at the beginning of the study was in some way affected by elevated BPb levels, then decreases in BPb levels, regardless of their source, were expected to lead to improvements in performance on global tests of cognition. Specifically, we expected larger decreases in BPb level to be accompanied by larger increases in the CI. The results suggest that this is the case during a 6-month period.

When age, initial levels of the relevant variables, change in ferritin, and background factors were controlled for, there was an increase of approximately 1 point on the CI for every decrease of 0.14 μmol/L (3 μg/dL) in BPb level. The size of the observed relationships of BPb level and cognitive performance is similar to the magnitude of the associations reported by Bellinger et al,[7] McMichael et al,[11] and Schwartz.[20] Although the amount of variance accounted for is not large, it is noteworthy that a positive cognitive effect associated with reducing BPb concentrations was detected in a group of children whose cognitive functioning could have been adversely affected by many nutritional and social factors before the study began and by multiple stresses during the study.

It might be argued that the lack of a concurrent relationship between BPb level and the CI at time 1 weakens inferences about a causal effect of declining BPb level on cognitive functioning. It would be consistent with previous findings in young children, however, to consider the CI at time 1 as a function of the child's earlier or accumulated exposure to lead rather than current BPb values. The fact that we found no significant results after 7 weeks but did so after 6 months suggests that the improvements

in cognitive performance were also related to the cumulative or delayed effects of decreasing BPb levels.

The mean values in Table 2 show that the CI increased between time 1 and time 2 and then tended to stay the same. Blood lead level tended to decrease most from time 1 to time 2 and then decreased very little thereafter. Yet the relationship of changes in CI to changes in BPb level were significant over the long term. The short-term increase in mean CI may be largely a practice effect, a phenomenon that would be less likely to occur during a 6-month period. The changes between time 1 and time 3, therefore, are probably a better assessment of fundamental changes. In any case, over the long term, there was considerable variation among the children with some children increasing and some decreasing in CI scores over time. It is this variability that is related to variability in the direction and degree of change in BPb.

One potential confounder was treatment for iron deficiency with resulting increases in iron levels during the course of the study. The case for a contribution of iron treatment is particularly strong, because a number of children were iron deficient and were treated with iron but not edetate calcium disodium and also because initial cognitive level was related to ferritin but not to BPb level. Using ferritin as the index of both deficiency and improvement, however, we found no evidence that increases in ferritin were related to improvements in cognitive performance.

The results of this study contribute to the understanding of the effects of moderate lead poisoning in young children and provides results that confirm and supplement those from a number of studies with different methods. It is not impossible that some unmeasured variable caused independent but parallel changes in BPb level and cognitive performance, and we must remain cautious in making causal attributions. The data are consistent, however, with the presence of an association between cognitive changes and changes in lead levels. Further research into the cognitive effects of chelation treatment and other forms of intervention is clearly needed.

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